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Diabetes Insipidus Associated With Langerhans Cell Histiocytosis: Is it Reversible?

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Fourteen of 58 (24%) children with Langerhans cell histiocytosis (LCH) currently attending the Hospital for Sick Children (London) developed thirst and polyuria during the course of their disease. Three had single-system disease confined to bone, and 11 had multisystem disease. The median age at presentation of LCH was 2 years 0 months, and polyuria/polydipsia developed at a median age of 3 years 9 months (range 1 month before diagnosis of LCH to 4 years after diagnosis). Each child had a water deprivation test with measurement of urinary arginine vasopressin (AVP) to document diabetes insipidus. The doses of 1-desamino-8-D arginine vasopressin (DDAVP) required to control symptoms were compared at diagnosis and at a mean follow-up of 7 years 8 months. Local and systemic treatment was recorded.

Ten of 14 children were shown to have ''complete'' diabetes insipidus, whilst the other four had ''partial'' diabetes insipidus. Seven children were treated with irradiation-with or without systemic chemotherapy, six with systemic chemotherapy only, and one with DDAVP replacement only. No child, including two with partial diabetes insipidus irradiated within 4 weeks of the onset of symptoms, lost symptoms of polyuria/polydypsia, and none was able to discontinue DDAVP replacement. One child treated with Etoposide showed a temporary rise in urinary AVP level to within the normal range but still needed DDAVP to control her symptoms. The mean doses of DDAVP at onset of diabetes insipidus and at follow-up were 9.3 µg and 18 µg daily, respectively.

We conclude that the most appropriate treatment for reversing diabetes insipidus complicating Langerhans cell histiocytosis is yet to be determined. Precise documentation of posterior pituitary dysfunction, including measurement of urinary AVP levels, is essential if the effects of new forms of treatment are to be assessed accurately. **Med. Pediatr. Oncol. 28:289–293.**

Key words: polyuria; polydipsia; AVP

INTRODUCTION

Diabetes insipidus is a common manifestation of Langerhans cell histiocytosis (LCH) although its reported frequency varies in different series [1–3]. The pathogenesis of the condition is not precisely understood. Infiltration of the hypothalamic pituitary axis by Langerhans-like cells has been reported in 50% of autopsied patients [4], and structural abnormalities are often seen in this region on gadolinium-enhanced magnetic resonance imaging (MRI) [5,6]. However, MRI shows no abnormality in some LCH patients with diabetes insipidus and other mechanisms of damage to the antidiuretic pathway such as the effect of cytokines diffusing from adjacent bony disease [7] or an autoimmune effect [8] could play a part.

In the past, study of the natural history of diabetes insipidus in LCH has been hampered by insensitive water deprivation tests which did not differentiate between varying degrees of posterior pituitary dysfunction. More recently, the ''short'' (7-hour) water deprivation test, with measurement of urinary arginine vasopressin (AVP), has been found to be more accurate and discriminating [9]. Partial diabetes insipidus does occur and its severity may fluctuate spontaneously [10], just as LCH in other organs is known to [11]. Pituitary irradiation is regarded as the ''standard treatment'' of diabetes insipidus in LCH with response defined informally as a reduction of symptoms and a decreased need for replacement 1-desamino-8-D arginine vasopressin (DDAVP) therapy. However, the original diagnosis of diabetes insipidus in these patients was usually based on clinical symptoms (thirst and polyuria) rather than on more objective laboratory-based diagnostic criteria. Some patients with apparent polyuria/polydypsia may not have developed true diabetes insipidus. Thus, partial diabetes insipidus may have spontaneously regressed in some patients.

Having documented diabetes insipidus in our patients by short water-deprivation test, we investigated the response to radiotherapy and to systemic chemotherapy.

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TABLE I. Patient Details, Water Deprivation Results, DDAVP Requirements, Treatment and Follow Up*

				Water-deprivation test		
Patient	Age at diagnosis of LCH	Systems involved in addition to pituitary/hypothal	Onset of DI	Osmolality (mosmol/kg) Urine	Plasma	Urine AVP pmol/L
EC	7 yrs 6 mths	Bone	11 yrs 6 mths	518	303	33.9
				After pituitary irradiation		<5
RG	6 mths	Bone, skin	4 yrs	597	289	16
				After pituitary irradiation		5.6
XC	2 yrs 10 mths	Bone	4 yrs 1 mth	96	309	16
TB	10 yrs	Bone	10 yrs	142	311	1.7
LG	2 yrs	Skin, bones, lungs	2 yrs 5 mths	180	323	7.2
LM	1 yr 2 mths	Bones, skin	2 yrs 4 mths	178	315	2.4
CS	2 yrs	Skin, ears, bones	4 yrs	137	315	4.0
LM	11 mths	Skin, bone, lungs	2 yrs 6 mths	318	303	28
				After VP16		75
				2 yrs after VP16		49.8
JA	12 mths	Skin, gums, ears Bone	2 yrs 1 mth	198	303	5.9
LJ	7 mths	Skin, bones, liver, spleen, bone marrow	3 yrs	169	301	
SL	1 yr 5 mths	Skin, ears, lungs	4 yrs 5 mths	630	278	34.6
RO	3 yrs	Lungs, ears, bones	4 yrs 5 mths	242	321	3.4
PH	2 yrs 6 mths	Skin, bones, ears, gums, lungs	3 yrs 5 mths	122	284	0.1
TN	2 yrs 11 mths	Skin, bones, lungs	3 yrs 9 mths	97	303	3.1

*RT, radiotherapy; VP16, etoposide; f, fractions (of radiotherapy); Gy, gray.

PATIENTS AND METHODS

Of a total of 68 patients with biopsy-proven LCH currently attending our hospital, 14 complained of thirst and polyuria at some time during their illness. There were seven girls and seven boys. At diagnosis of LCH (median age 2 years) three children had single-system disease, confined in each case to bone, and 11 had multisystem disease. To document posterior pituitary function each had a 7-hour water deprivation test with measurement of plasma and urine osmolality and urinary AVP levels. The median age of onset of diabetes insipidus was 3 years 9 months (range from 1 month before diagnosis to 4 years after diagnosis). Criteria for diagnosis of ‘‘complete’’ diabetes insipidus were (a) urine osmolality <300 mosml/kg with plasma osmolality >295 mosml/kg and/or (b) urinary AVP less than 10 pmol/L, after 7 hours of water deprivation. For a diagnosis of ‘‘partial’’ diabetes insipidus, urinary AVP levels of between 10 and 70 pmol/L were required [9]. The dose of DDAVP required to control symptoms was documented at diagnosis and after a mean follow-up of 7 years 8 months (range 12 months to 13 years). The treatment received by each child during this follow-up period was noted.

RESULTS

Of the 14 patients presenting with thirst and polyuria, ten had ‘‘complete’’ diabetes insipidus with urinary AVP ranging from 0.1 to 7.2 pmol/L, plasma osmolality from 284 to 323 mosml/kg, and urine osmolality from 92 to 242 mosml/kg after 7 hours of water deprivation (see Table I). Four children, indistinguishable on symptoms alone, had ‘‘partial’’ DI with urinary AVP ranging from 16 to 34 pmol/L, plasma osmolality ranging from 289 to 303 mosml/kg, and urine osmolality ranging from 318 to 630 mosml/kg.

All 14 children received DDAVP replacement therapy. In addition, seven had some form of systemic therapy for their LCH in the period after the diagnosis of diabetes insipidus; three received Etoposide or Vincristine alone or combined with Prednisolone, and four received Prednisolone alone. Four were treated with pituitary directed irradiation only. Two children with ‘‘partial’’ diabetes insipidus (urinary AVP 33.9 pmol/L and 16 pmol/L) were irradiated within 4 weeks of onset of thirst and polyuria. Subsequent testing of these two children at 10 weeks and 6 months, respectively, after irradiation, showed them to have developed ‘‘complete’’ diabetes insipidus with urinary AVP values of <5 pmol/L and 5.6 pmol/L, respectively. Two other children received irradiation which included the pituitary/hypothalamic axis, both for retro-orbital disease. One child received whole cranial irradiation for extensive bony disease as well as systemic chemotherapy. One child with ‘‘partial’’ diabetes insipidus (urinary AVP 28 pmol/L) was treated with Etoposide. A repeat water-

Table 1. (Continued)

DDAVP dose at onset	Treatment	Length of follow-up	DDAVP dose at last follow-up
2.5 μg bd	Pituitary RT 12 Gy/8 f/10 days within 3 weeks of symptom onset	7 yrs	20 μg bd
2.5 μg bd	Pituitary RT 12 GY/8 f/10 days within 4 weeks of symptom onset	5 yrs	2.5 μg tds
Syntopressin 5 units qds	Pituitary RT 10 Gy/10 f/14 days	8 yrs 9 mths	5 μg bd
5 μg bd	Pituitary RT 12 Gy/8 f/11 days within 5 mths of symptom onset	5 yrs	20 μg bd
2.5 μg tds	Lateral opposed field RT to retro-orbital region 12 Gy/7 f/8 days	5 yrs 6 mths	5 μg bd
5 μg bd	Lateral opposed field RT to retro orbital region 10 Gy/6 f/8 days	8 yrs	10 μg bd
7.5 μg mane	Vincristine, VP16, prednisolone	8 yrs	20 μg bd
10 μg nocte	Whole cranial RT 12 Gy total dose: fractions and time scale unknown		
2.5 μg bd	Prednisolone VP16	5 yrs	5 μg bd
2.5 μg bd	VP16	1 yr	2.5 μg bd
2.5 μg bd	Prednisolone	9 yrs	5 μg bd
5 μg bd	Prednisolone	6 yrs	5 μg bd
5 μg bd	Prednisolone	8 yrs	10 μg bd
5 μg bd	Prednisolone	8 yrs	5 μg tds
5 μg bd	Replacement anterior pituitary hormones	6 yrs 5 mths	5 μg tds

deprivation test showed her to have a urinary AVP within the normal range (75 pmol/L), but she still experienced thirst and polyuria if her DDAVP was stopped and when tested 2 years later, her urinary AVP was again in the ‘‘partial’’ diabetes insipidus range (49.8 pmol/L).

Symptoms of diabetes insipidus persisted in all 14 children, and all required long-term DDAVP replacement. The mean starting dose of DDAVP required to control polyuria and polydypsia was 9.3 μg daily, most children requiring between 2.5 and 5 μg bd. At follow-up the mean daily dose of DDAVP was 18 μg, with most children requiring between 5 and 20 μg bd.

DISCUSSION

Diabetes insipidus is a common complication of LCH. Until recently, biochemical documentation was cumbersome and inaccurate, but the ‘‘short’’ water-deprivation test, with measurement of urinary AVP, is an accurate and sensitive test which can discriminate between partial and complete deficiency of vasopressin. Thirst and polyuria may occur with only partial vasopressin deficiency and may remit spontaneously. For instance two of five patients in one series went on to develop complete diabetes insipidus, but two remained stable without symptoms and one spontaneously recovered full function [10]. This observation suggests that reported responses to treatment may, in fact, represent spontaneous regression of partial hormone deficiency. There is also the possibility that some reported responses were in patients whose diagnosis was made on clinical symptoms of polyuria/polydypsia only and who did not in fact have diabetes insipidus but some other cause for their symptoms.

In Greenberger’s series [12], 28 of 127 patients with LCH developed diabetes insipidus. The diagnosis was based on clinical features, low random urine osmolality, and response to DDAVP. Twenty-one received pituitary irradiation of 3–7 Gy over 3–7 days. Four patients, three of whom had been irradiated within 1 week of developing symptoms, subsequently stopped DDAVP replacement, and four were able to reduce their dose of DDAVP, albeit temporarily in one case. Clinically the report does not record whether any of these patients also received systemic therapy.

Of 1,200 patients with a diagnosis of LCH treated at the Mayo Clinic over a 40-year period [13], 45 (3.7%) developed diabetes insipidus. In 21 cases the diagnosis was made only on clinical grounds, and, although another 24 patients had standard water deprivation tests, these results are not recorded here. Twenty-eight patients, eight of whom also received chemotherapy, were treated with pituitary irradiation. The other 17 patients received no radiotherapy, but 11 received chemotherapy (usually Vinblastine alone or with Prednisolone). Five patients in the irradiated group had complete clinical response, whereas none of the 17 unirradiated patients re-

TABLE II. LCH and Diabetes Insipidus: Incidence, Diagnostic Criteria and Response to Therapy in Published Series

First author (Ref)	Total patients with LCH	Number (%) with DI	Diagnostic criteria for DI	Number treated with Radiotherapy	Number treated with Chemotherapy	'Response' R (%)	'Response' C (%)
Greenberger (12)	127	28 (22)	Clinical	21	7	4	0
Minehan (13)	1200	45 (3.7)	Clinical 21 St WDT 24	28	17	5	0
Grois (1)	199	19 (9.5)	Clinical 12 Short WDT 7	5	19	0	0
Ceci (2)	90	18 (20)	?	?	18	0	0
This series	58	14 (24)	Short WDT Urinary AVP	7	6	0	0
Totals	1664	124 (7.4)		61	67	9 (15)	0

St WDT = standard water deprivation test; AVP = Arginine vasopressin, R = radiotherapy; C = Chemotherapy; DI = diabetes insipidus

sponded. Of the five responders, four were irradiated within 14 days of developing symptoms. There was no obvious relationship between normalization of CT/MRI scans and resolution of diabetes insipidus. The authors reviewed the literature and noted a 20% response rate in patients who had received pituitary/hypothalamic irradiation compared with a 7% response rate in nonirradiated patients.

In the DAL-HX 83 series reported by Grois et al. [1], in which 19 out of 199 patients (9.5%) developed diabetes insipidus, all patients were treated with chemotherapy and five received irradiation in addition. In none of the patients was diabetes reversed by treatment. Similarly, in the Italian cooperative series [2] 20% patients developed diabetes insipidus, all were treated with chemotherapy and none responded. The number who were also irradiated in this series is not stated (see Table II).

In our series, seven of 14 children with LCH and carefully documented diabetes insipidus received irradiation either specifically directed to the hypothalamic/pituitary axis or encompassing it, and six received systemic chemotherapy only. All 14 children continued to suffer thirst and polyuria and, with a mean follow-up from diagnosis of diabetes insipidus of 7 years 8 months, all needed continuing DDAVP replacement. Two children with partial diabetes insipidus received pituitary irradiation within 4 weeks of developing symptoms and on subsequent testing had developed complete diabetes insipidus. One child, initially documented to have partial diabetes insipidus at onset, was treated with Etoposide and showed temporary increase in urinary AVP to normal levels. However, she continued to have polyuria/polydipsia and needed replacement DDAVP; subsequent testing showed her urinary AVP to have reverted to the partial diabetes insipidus range.

Is diabetes insipidus caused by LCH ever reversible? As a first step toward answering this question accurate documentation of posterior pituitary function is essential and is now possible through modern ''discriminatory'' water-deprivation tests such as we have used in this series. Early therapeutic intervention is perhaps more likely to be successful in patients who have residual posterior pituitary function. The role of high-resolution MRI with gadolinium enhancement in predicting patients at risk of diabetes insipidus could be addressed systematically by serial scanning alongside accurate water-deprivation testing.

The best form of treatment for preventing or delaying the onset of diabetes insipidus still has to be determined, but the first International LCH treatment trial (LCH I) [14] will provide crucial data on the relative efficacy of Etoposide and Vinblastine. If one agent proves superior to the other, a subsequent study could examine the possibility that a ''dose-response'' effect might be achieved by altering the dose and or scheduling of that agent. The possibility of a dose-response effect of chemotherapy is suggested by the DALHX 83 study [1] in which the recorded incidence of diabetes insipidus is considerably lower than in studies in which less intensive chemotherapy was used [3].

In the meantime the traditional role of radiotherapy with its potential for anterior pituitary damage and induction of second malignancy needs careful consideration when the response rate, at best, is likely to be 20%.

REFERENCES

1. Grois N, Flucher-Wolfram B, Heighter A, et al.: Diabetes Insipidus in Langerhans cell histiocytosis: results from the DAL-HX 83 study. Med Pediatr Oncol 24:248–256, 1995.
2. Ceci A, de Terlizzi M, Colella R, et al.: Langerhans Cell Histiocytosis in childhood: results from the Italian Cooperative AIEOP-CNR-H.X 83 study. Med Pediatr Oncol 21:265–270, 1993.
3. McClelland J, Broadbent V, Yeomans E, et al.: Langerhans cell histiocytosis; a conservative approach to treatment. Arch Dis Child 65:301–303, 1990.
4. Vawter GF, Greenberger JS, Crocker AC: A retrospective clinicopathologic analysis of diabetes insipidus in dendritic cell disease. Med Pediatr Oncol 14:112, 1986.
5. Broadbent V, Dunger DB, Yeomans E, Kendall B: Anterior pituitary function and CT/MR imaging in patients with Langerhans cell histiocytosis and diabetes insipidus. Med Pediatr Oncol 21: 31–35, 1993.

6. Rosenfield NS, Abrahams J, Komp D: Brain MR in patients with Langerhans cell histiocytosis: findings and enhancement with Gd-DPTA. Pediatr Radiol 20:433–436, 1990.
7. Kannourakis G, Abbas A: The role of cytokines in the pathogenesis of Langerhans cell histiocytosis. Br J Cancer 70(Suppl xxiii): 37–40, 1994.
8. Scherbaum WA, Wass JAH, Besser GM, et al.: Autoimmune cranial diabetes insipidus: its association with other endocrine diseases and with histiocytosis X. Clin Endocrinol 25:411–420, 1986.
9. Dunger DB, Seckl JR, Grant DB, et al.: A short water deprivation test incorporating urinary arginine vasopressin estimations for the investigation of posterior pituitary functionin children. Acta Endocrinol (Copenh) 117:13–18, 1988.
10. Dunger DB, Broadbent V, Yeomans E, et al.: The frequency and natural history of diabetes insipidus in children with Langerhans cell histiocytosis. N Engl J Med 321:157–162, 1989.
11. Broadbent V, Pritchard J, Davies G, et al.: Spontaneous remission of multisystem histiocytosisX. Lancet 1:253–254, 1984.
12. Greenberger JS, Crocker AC, Vawter G, et al.: Results of treatment of 127 patients with systemic histiocytosis. Medicine (Baltimore) 60:331–338, 1986.
13. Minehan KJ, Chen MG, Zimmerman D, et al.: Radiation therapy for Diabetes insipidus caused by Langerhans cell histiocytosis. Int J Radiat Oncol Biol Phys 23:519–524, 1992.
14. Ladisch S, Gadner H: Treatment of Langerhans cell histiocytosis evolution and current approaches. Br J Cancer 70(Suppl xxiii):41–46, 1994.